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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/262,126	03/03/1999	BRIAN S. MILLER	GC396-2	8961

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EXAMINER	
RAO, MANJUNATH N	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 01/27/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/262,126	MILLER ET AL.	
	Examiner	Art Unit	
	Manjunath N. Rao, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *5-10,12,14,15,27-40 and 52-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *9,10,12,31 and 32* is/are allowed.

6)☒ Claim(s) *5-8, 14, 15, 27-30, 33-40, 52-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Prosecution Application

The request filed on 9-16-02 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/262126 is acceptable and a CPA has been established. An action on the CPA follows.

Claims 5-10, 12, 14-15, 27-40 and 52-57 are currently pending and present for examination in this application.

Applicants' amendments and arguments filed on 9-16-02, paper No.29, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 55 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 55 recites the phrase "wherein the deletion is obtained from a pullulanase" which is unclear to the Examiner. It is not clear to the Examiner as to how one can "obtain a deletion". It appears that applicants either meant "the deletion is made to a pullulanase having amino acid SEQ ID NO:2" or "the truncated pullulanase is obtained from a pullulanase having amino acid sequence shown in SEQ ID NO:2". If this is so amending the claim accordingly would overcome the above rejection.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 5-8, 14-15, 27-30, 33-40, 52-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Deweer et al. (US 6, 074, 854 filed 12-23-97, issued 6-13-2000) and McPherson et al. (Biochemical Soc. Trans., 1988, vol. 16(5) :723-724) or Albertson (Biochim. Biophys. Acta, Vol. 1354:35-39, 1997).

This rejection is based on printed publications and a patent. Claims 5-8, 14-15, 27-30, 33-40, 52-57 in this instant application are drawn to a modified pullulanase from *B.deramificans* T89.117D, wherein the modification is a deletion of about 100, 200 or 300 amino acids from the amino terminus, wherein the modified pullulanase is produced by culturing a host cell comprising a nucleic acid which is at least 70% identical to SEQ ID NO:1 encoding a truncated pullulanase wherein the host cell is *B.licheniformis* in which certain proteases are inactivated or eliminated. The claims are also drawn to compositions comprising the above modified pullulanase and compositions further comprising additional enzymes such as glucoamylase isolated from *Aspergillus* strains and wherein the modified pullulanase is 60 or 80% of the composition and wherein the composition is in the solid or liquid form.

Deweer et al. teach a modified pullulanase --wherein the first 29 amino acids are removed-- obtained from a Gram positive bacteria such as *B.deramificans* T89.117D produced

by a method of culturing a host cell such as *B.licheniformis* in which certain protease genes have been inactivated. The reference also teaches the method of making the recombinant enzyme by obtaining the host cell transformed with a polynucleotide having at least 70% identity to SEQ ID NO:1 (see sequence alignment sent in the previous office action). The reference teaches the compositions either in the solid form or liquid form comprising pullulanase wherein it is of the order of 60% of the total enzyme concentration. The reference also teaches compositions comprising additional enzymes such as glucoamylase isolated from *Aspergillus* strains (see claims in the reference). However, the reference does not teach modification of pullulanase by way of deletion of about 100, 200 or 300 N-terminal amino acids.

McPherson et al. teach that pullulanases are significantly large enzymes when compared to other polysaccharide hydrolases and that this large size reduces the efficiency with which it can function by restricting access to internal alpha 1,6 bonds within highly branched substrates. The reference teaches that proteolytic digestion and computer-based sequence analyses are being used in the art to define a functional "core" pullulanase. The reference provides sources for such computer based homology searches. As an example the reference provides a schematic illustration of the relative position of the 5 conserved "amylase" regions within a selection of hydrolases in comparison to the *K.pneumoniae* pullulanase. The reference teaches that the long N-terminal region lacks any polysaccharide binding or catalyzing sites. McPherson et al. teach the modification of deleting nearly 170 amino acid residues from the amino terminal end which leads to approximately 30% higher activity than that of the native enzyme.

Albertson et al. also teach the modification of a pullulanase (from *C.saccharolyticus*), wherein nearly 381 nucleotides from the 5' region of the cDNA encoding a pullulanase was

deleted resulting in a N-terminal truncated pullulanase. The reference also teaches that the deleted amino acid sequence is not essential for either activity or thermostability.

While both McPherson et al. and Albertson et al. do not teach a pullulanase isolated from a Bacillus, it appears that experiments involving truncation of N-terminal amino acids in pullulanase enzymes was well known in the art. These experiments appears to have been performed to determine the nature and the location of secretion signal, activity, catalytic site, transport across membrane and secretion into liquid medium.

It would have been obvious to one skilled in the art at the time the invention was made to combine the teachings of Deweer et al. with that of McPherson et al. or Albertson et al. to make a modified pullulanase in which N-terminal amino acids have been deleted. This is because Deweer et al. teach a pullulanase isolated from a Bacillus, *B.deramificans*, which is a very large size enzyme with more than 900 amino acids. McPherson et al. teach a method of increasing the efficiency of large size pullulanase by determining and deleting non-essential amino acids in the N-terminal region and Albertson et al. and McPherson et al. teach that deletion of up to at least 100-300 amino acids does not affect the activity of the enzyme negatively but on the other hand increases the efficiency of the enzyme by nearly 30%. It would also be obvious for one skilled in the art to eliminate or inactivate protease genes in the expression hosts, such as Carlsberg protease or endo Glu C protease as Deweer et al. teach such inactivation of proteases such that the heterologous protein is not digested by the endogenous proteases.

Based on the above teachings, one of ordinary skill in the art would be motivated to delete up to 300 amino acids as McPherson et al. compare and show that N-terminal regions of large pullulanase do not have any conserved sequences for either activity or binding to

polysaccharide and cleavage of such non-essential sequences results in higher efficiency of the enzyme and Albertson et al. teach a pullulanase in which N-terminal amino acids have been deleted. One would have a reasonable expectation of success since Deweer et al. provide the nucleic acid encoding the pullulanase from *B.deramificans* in a host cell such as *B. licheniformis* in which protease genes have been inactivated and also provide the compositions comprising up to 60% of pullulanase.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

In response to the final rejection of the above claims previously, applicants have traversed the above rejection. Contrary to applicants argument, the reference of McPherson et al. is aimed at all pullulanases in general even though some of its focus is on the pullulanase of *Klebsiella*. The reference clearly teaches that pullulanases in general are large enzymes and that truncation of pullulanases generally leads to an increase in the efficiency of the enzyme by 30%. That teaching by itself and also due to the well known fact in the art that pullulanases have industrial application would have motivated one of ordinary skill in the art to produce truncated pullulanase from large size pullulanases regardless of its source.

Albertson et al. also teach a similar aspect of pullulanases and even compare sequences from Bacillus and other bacterial species. Applicants argue at length that in addition to the conserved regions revealed by Albertson et al., they have disclosed two other conserved regions and those regions are not taught by Albertson et al. Applicants also argue that they further disclose that the limits of amino acid truncations in the N-terminus of pullulanase would not go

beyond the "Y" region. However, such arguments are moot as claims are not directed to identification or disclosure of conserved regions of pullulanases.

While applicants have argued against the rejection in response to the final rejection, they have not responded against the Examiner's response in his advisory action. Therefore, for all the above reasons, Examiner continues to maintain the above rejection of claims under 35 U.S.C. 103(a) as being *prima facie* obvious.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

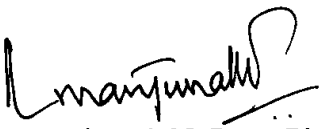
Allowable Subject Matter

Claims 9-10, 12, 31, 32 are allowable.

The following is a statement of reasons for the indication of allowable subject matter: Following a diligent search it was determined that the prior art neither teaches nor suggests a truncated *Bacillus* pullulanase in which 98 amino acids or specifically 102 amino acids are delet4ed from the N-terminus. Similarly, prior art does not teach or suggest a modified *Bacillus* pullulanase wherein the modification comprises addition of at least one amino acid to the N-

terminal of the mature pullulanase and wherein the added amino acid is specifically alanine. While prior art does teach truncation of pullulanases up to 100 or up to 300 N-terminal amino acids such that the efficiency of the enzyme can be increased by as much as 30%, Examiner was unable to find motivation in the art to specifically delete either 98 or 102 amino acids from the N-terminal end with glutamic acid as the starting amino acid . Therefore the above claims are indicated as allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath Rao whose telephone number is (703) 306-5681. The Examiner can normally be reached on M-F from 7:30 a.m. to 4:00 p.m. If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, P.Achutamurthy, can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Manjunath N. Rao. Ph.D.
January 23, 2003